SATURATION EFFECTS ON T-CELL ACTIVATION IN A MODEL OF A MULTI-STAGE PATHOGEN

MICHAEL SHAPIRO AND EDGAR DELGADO-ECKERT

Abstract. In [5], we studied host response to a pathogen which uses a cycle of immunologically distinct stages to establish and maintain infection. We showed that for generic parameter values, the system has a unique biologically meaningful stable fixed point. That paper used a simplified model of T-cell activation, making proliferation depend linearly on antigen-T-cell encounters. Here we generalize the way in which T-cell proliferation depends on the sizes of the antigenic populations. In particular, we allow this response to become saturated at high levels of antigen. As a result, we show that this family of generalized models shares the same steady-state behavior properties with the simpler model contemplated in [5].

1. Introduction

Pathogens that cyclically traverse different stages during their life cycle or during an infection process have been studied since the late nineteenth century. Important examples are *Plasmodium* ([6]), Trypanosoma ([16]), and the family of herpes viruses, including the Epstein-Barr virus (EBV) ([15], [14]). One remarkable characteristic of infections with many of such pathogens is life-long persistent infection ([8], [15], [10], [6], [16]).

In [5], we introduced a model of a pathogen that uses a cycle of n antigenically distinct stages to establish and maintain infection. The model is given by $2n$ differential equations,

$$\begin{aligned} \frac{dS_j}{dt} &= F_j(S,T) = r_{j-1}f_{j-1}S_{j-1} - a_jS_j - f_jS_j - p_jS_jT_j \\ \frac{dT_j}{dt} &= G_j(S,T) = c_jS_jT_j - bT_j. \end{aligned} \tag{1}$$

Here S_j denotes the pathogen population at stage j, T_j is the cognate host response. The indices $j = 0, \ldots, n-1$ are taken modulo n. The parameters represent the following processes:

- a_j is the decay rate of stage S_j. If a_j is negative, this state proliferates.
- f_j is the rate at which stage S_j is lost to become (or produce) stage S_{j+1}.
- r_j is an amplification factor in the process by which stage S_j becomes (or produces) stage S_{j+1}. For example, the loss of one lytically infected cell may produce $r_j \cong 10^4$ free virus.
- p_j represents the efficacy of the immune response T_j in killing infected stage S_j.
- c_j is the antigenicity of stage S_j, i.e., its efficacy in inducing proliferation of immune response T_j.
- b is the natural death rate of the response T_j. We assume it is the same for all stages.

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We refer to the parameters collectively as θ. Except for a_j, $j = 0, \ldots, n-1$, these are assumed non-negative.

Our flagship result is that while (1) has 2^n fixed points for generic values of θ, exactly one of these is biologically meaningful and stable ([5]).

Let us focus for the moment on the terms $-p_j S_j T_j$ of F_j and $c_j S_j T_j$ of G_j. The term $-p_j S_j T_j$ represents the killing of pathogen at stage j (usually infected cells in a particular differentiation state) by the cognate T-cell population. This takes place pursuant to an encounter between T-cells and infected cells displaying antigen complexed to MHC. To a first approximation the rate of such encounters is proportional to the product of the sizes of the two populations. Thus, to a first approximation, this term reflects the mechanism of the biological process it represents.

The term $c_j S_j T_j$ of G_j represents proliferation of T-cells in response to the presence of antigen. Here, the underlying biological processes are considerably more complicated, involving a number of cell types. Initially, T-cells are activated and begin to proliferate only in response to antigen presenting cells, particularly dendritic cells (DCs) ([12]). The density of presented antigen is known to affect these T-cell-DC interactions ([7], [19]), eliciting differing CTL responses at different densities, including T-cell exhaustion at high concentrations of presented antigen ([11]). Activated CD8+ T-cells also exhibit central and effector memory phenotypes and the relationships between these phenotypes is not well understood ([4]). Finally, the length of the cell cycle places a hard limit on the rate at which the T-cell population can proliferate. Thus, the rate of T-cell proliferation becomes *saturated* for large amounts of antigen ([9]). In this, they bear a similarity to the rates of enzyme catalyzed chemical reactions (reviewed in [2], see [3] for experimental evidence).

To accommodate dose-dependent effects, we will study the system

$$\begin{aligned} \frac{dS_j}{dt} &= \widehat{F}_j(S,T) = r_{j-1} f_{j-1} S_{j-1} - a_j S_j - f_j S_j - p_j S_j T_j \\ \frac{dT_j}{dt} &= \widehat{G}_j(S,T) = \varphi_j(S_j) T_j - b T_j. \end{aligned} \tag{2}$$

which generalizes (1). The function $\widehat{H}$ is unchanged from H. The terms of $\widehat{G}_j$ represent proliferation of CTLs in response to the presence of antigen and the loss of CTLs due to death or decommissioning. We use functions $\varphi_j : [0,\infty) \to [0,\infty)$ to denote the dose-response curves. We assume that for each j, $\varphi_j(0) = 0$, and that for $x \in (0,\infty)$, $\varphi_j'(x)$ exists and is positive. In particular, each φ_j is continuous on $[0,\infty)$ and strictly monotone increasing. The possibility of dose-response saturation arises from the case where there is an $m_j \in \mathbb{R}$ so that $\lim_{x\to\infty} \varphi_j(x) = m_j$. We show that with appropriate modification, the major results of [5] hold for (2). While the term $\varphi_j(S_j)$ is still phenomenological in that it omits discussion of biological mechanism, we argue in Section 4 that it may well offer a way to address this limitation.

The system (2) can exhibit a behavior which does not arise with (1). In either case if $a_j + f_j < 0$, we say that j is *self-establishing*. It is not hard to see that a self-establishing stage which is not regulated will expand without bound. On the other hand, as we will show, if $m_j \leq b$, the host cannot mount a response to S_j. It is *immuno-incompetent* with respect to this stage. If j is self-establishing and the host is immuno-incompetent with respect to j, we say that the parameter set is *fatal*. If the host is immunologically incompetent at all stages we say the host is *totally immunologically incompetent*. Clearly, in this case, if the basic reproductive number of the pathogen is greater than one, infection is also fatal to the host. Accordingly, we will assume that the host is immuno-competent for at least one stage.

2. Background and definitions

We start by transforming (2) through a change of coordinates. For this purpose we take $m_j := \lim_{x\to\infty}\varphi_j(x) \in \mathbb{R}\cup\{\infty\}$. Notice that if $m_j > b$, there is a unique value $b_j \in \mathbb{R}$ so that $\varphi_j(b_j) = b$. If $m_j \le b$, we take $b_j := \infty$. So we define

$$c_j := \begin{cases} \varphi_j'(b_j) & \text{if } b_j < \infty \\ 1 & \text{otherwise} \end{cases}$$

In the former case, c_j is the marginal antigenicity of S_j at the value b_j. We now use the linear change of coordinates

$$H : \mathbb{R}^{2n} \to \mathbb{R}^{2n}$$
$$(S_j, T_j) \mapsto (\overline{S}_j, \overline{T}_j) := H_j(S_j, T_j) := (c_j S_j, p_j T_j).$$

This gives the equations

$$\begin{aligned} \frac{d\overline{S}_j}{dt} &= \overline{\widehat{F}_j}(\overline{S},\overline{T}) = \overline{r}_{j-1} f_{j-1}\overline{S}_{j-1} - a_j\overline{S}_j - f_j\overline{S}_j - \overline{S}_j\overline{T}_j \\ \frac{d\overline{T}_j}{dt} &= \overline{\widehat{G}_j}(\overline{S},\overline{T}) = \overline{\varphi}_j(\overline{S}_j)\overline{T}_j - b\overline{T}_j \\ \overline{r}_j &= \frac{c_{j+1}}{c_j} r_j \\ \overline{\varphi}_j(\overline{S}_j) &= \varphi_j\left(\frac{S_j}{c_j}\right) \end{aligned} \tag{3}$$

Note that for each j, $\overline{\varphi}_j$ still enjoys the properties that it is differentiable, $\overline{\varphi}_j'(x) > 0$ for $x > 0$ and $\overline{\varphi}_j(0) = 0$. We now take $\overline{b}_j$ to be the unique solution to $\overline{\varphi}_j(\overline{b}_j) = b$, i.e., $\overline{b}_j := c_j b_j$, where such exists. Note that $\overline{\varphi}_j$ now enjoys the additional property that $\overline{\varphi}_j'(\overline{b}_j) = 1$. In the case studied in [5], $\varphi_j(S_j) = c_j S_j$ and thus $\overline{\varphi}_j(S_j) = S_j$, giving

$$\begin{aligned} \frac{d\overline{S}_j}{dt} &= \overline{\widehat{F}_j}(\overline{S},\overline{T}) = \overline{r}_{j-1} f_{j-1}\overline{S}_{j-1} - a_j\overline{S}_j - f_j\overline{S}_j - \overline{S}_j\overline{T}_j \\ \frac{d\overline{T}_j}{dt} &= \overline{\widehat{G}_j}(\overline{S},\overline{T}) = \overline{S}_j\overline{T}_j - b\overline{T}_j \end{aligned} \tag{4}$$

We will henceforth drop the bars and assume our equations are given in the form (3). We take a parameter set θ to be a set of values for b, r_j, f_j, a_j, m_j and b_j, $j = 0, ..., n-1$. When we need to make an explicit comparison with the φ_j of (2), we will refer to the later as "biological φ", φ_j^{bio}.

We will adopt the following notational conventions. Sets such $[j,k]$ and $[j,k)$ are to be taken cyclically. That is to say, if $j < k$, then $[j,k] = \{j,\dots,k\}$, while if $j > k$, $[j,k] = \{j,\dots,n-1,0,\dots,k\}$. We take $[j,j)$ to be the empty set so that any product taken over $[j,j)$ is equal to one. We abuse notation by taking $[0,n) = \{0,\dots,n-1\}$

We now review and in some cases generalize the definitions of [5].

Definition 1. Given a fixed point (S^*,T^*) of (3), the *regulated* and *unregulated* stages of (S^*,T^*) are

$$\text{Reg}(S^*,T^*) = \{j \mid T_j^* \neq 0\}$$
$$\text{Unreg}(S^*,T^*) = \{j \mid T_j^* = 0\}$$

Definition 2. (S^*, T^*) is *biologically meaningful* if $S_j^* \geq 0$, $T_j^* \geq 0$ for $j = 0, \ldots, n-1$. It is *infected* if for some (hence, all, see 1) below) j, $S_j^* > 0$.

Definition 3. Given a parameter set θ, the *self-establishing* stages are

$$\mathrm{SE}(\theta) = \{j \mid a_j + f_j < 0\}.$$

Definition 4. The *immuno-incompetent* stages of θ are

$$\mathrm{Incomp}(\theta) = \{j \mid m_j \leq b\} = \{j \mid b_j = \infty\}.$$

Definition 5. If $j \in \mathrm{SE}(\theta) \cap \mathrm{Incomp}(\theta)$, we say that the stage j and the parameter set θ are *fatal*. We will assume that the host is capable of mounting a response to at least one stage, i.e., $\mathrm{Incomp}(\theta) \neq [0, n)$.

Definition 6. If $\mathrm{SE}(\theta) = \emptyset$, the *follow-on* constants of θ are

$$M_j = \frac{r_j f_j}{a_{j+1} + f_{j+1}}$$
$$M_{jk} = \prod_{\ell \in [j,k)} M_\ell$$

In the case where $\mathrm{SE}(\theta) \neq \emptyset$, M_j is only *meaningful* for our purposes for $j+1 \notin \mathrm{SE}(\theta)$. Accordingly, M_{jk} is only *meaningful* if $(j, k] \cap \mathrm{SE}(\theta) = \emptyset$. Note that for every $k \in [j, \ell)$ it holds $M_{j\ell} = M_{jk} M_{k\ell}$.

Definition 7. We say that j *starves* k and write $j \succ k$ if $b_j M_{jk} < b_k$. Here we assume that M_{jk} is meaningful and that b_j is finite, though b_k need not be. In particular, if M_{jk} is meaningful, $j \notin \mathrm{Incomp}(\theta)$, and $k \in \mathrm{Incomp}(\theta)$, then $j \succ k$.

Definition 8. The *starvable* stages of θ are

$$\mathrm{Str}(\theta) = \{k \mid \text{there is } j \text{ so that } j \succ k\}.$$

The *unstarvable* stages $\mathrm{Unstr}(\theta)$ are the complement of these.

Definition 9. A biologically meaningful fixed point (S^*, T^*) is *saturated*[1] if $\mathrm{Reg}(S^*, T^*) = \mathrm{Unstr}(\theta)$. It is *moderated* if for $j \in \mathrm{Unreg}$, $S_j^* < b_j$.

Definition 10. If $\mathrm{SE}(\theta) = \emptyset$, we define

$$R_0 = \prod_{j=0}^{n-1} M_j.$$

R_0 may be interpreted as the number of copies of the pathogen produced by a single copy entering a naive host ([5]). It is not hard to see that R_0 is invariant under the transformation H as befits a property of the organism being described.

Definition 11. When we say that θ is *generic* we will require the following:

- $R_0 \neq 1$.
- There is no j so that $a_j + f_j = 0$.
- There is no pair (j, k) so that $b_j < \infty$, $b_k < \infty$ and $b_j M_{jk} = b_k$.
- At the saturated biologically meaningful fixed point, there are j and k so that $T_j^* \neq T_k^*$.

[1] There is an unfortunate collision here between the use of the term saturated to denote the host mounting a T-response to all stages capable of supporting one ([5]) and the meaning of the term used in the Introduction above, namely, a maximum prolfieration rate, with no increase through further stimulation.

It is not hard to see that each of these conditions has measure zero, thus justifying the use of the term generic. The detailed motivation for these exclusions can be found in [5].

Definition 12. Suppose $\mathrm{Reg}(S^*, T^*) \neq \emptyset$. Given a stage k, we define h_k to be the unique stage such that $h_k \in \mathrm{Reg}(S^*, T^*)$ and $(h_k, k) \subset \mathrm{Unreg}(S^*, T^*)$.

3. Results

We will start by assuming that $\mathrm{SE}(\theta) = \emptyset$. This will be a standing assumption until it is lifted in Section 3.1.

The linear stability analysis performed in [5] is possible because we were able to calculate the characteristic polynomial of the Jacobian matrix of the right hand side of (4), which corresponds to setting $\varphi_j(S_j) = S_j$ for each j in (3) (recall that we are omitting the bars). Here we contemplate more general $\varphi_j : \mathbb{R} \to \mathbb{R}$, $j = 0, ..., n-1$ (which is a consequence of contemplating more general $\varphi_j^{\mathrm{bio}} : \mathbb{R} \to \mathbb{R}$) with the properties mentioned above. Consequently, in order to make use of the results obtained in [5], we need to establish what changes are induced on the Jacobian matrix through the use of more general functions φ_j. The partial derivatives of the right hand side of (3) are given by

$$\frac{\partial \widehat{F}_k}{\partial S_j} = \begin{cases} r_{k-1} f_{k-1} & \text{if } j = k-1 \\ -a_k - f_k - T_k & \text{if } j = k \\ 0 & \text{otherwise} \end{cases}$$

$$\frac{\partial \widehat{F}_k}{\partial T_j} = \begin{cases} -S_k & \text{if } j = k \\ 0 & \text{otherwise} \end{cases}$$

$$\frac{\partial \widehat{G}_k}{\partial S_j} = \begin{cases} \varphi_k'(S_k) T_k & \text{if } j = k \\ 0 & \text{otherwise} \end{cases}$$

$$\frac{\partial \widehat{G}_k}{\partial T_j} = \begin{cases} \varphi_k(S_k) - b & \text{if } j = k \\ 0 & \text{otherwise} \end{cases}$$

Since the functions $\widehat{F}_j$ do not depend on any φ_j, only the partial derivatives $\frac{\partial \widehat{G}_k}{\partial S_j}$ and $\frac{\partial \widehat{G}_k}{\partial T_j}$ differ from the results obtained in [5]. As we shall see, most differences vanish when the functions are evaluated at a fixed point.

Proposition 13.

(1) *R_0 is the basic reproductive number of the pathogen.*
(2) *If $R_0 < 1$, the pathogen fails to establish infection and $(S^*, T^*) = 0$ is a local attractor. If $R_0 > 1$, the pathogen is able to establish infection. In particular, this makes $(S^*, T^*) = 0$ an unstable fixed point.*
(3) *If $R_0 < 1$, $(S^*, T^*) = 0$ is a global attractor.*

Proof. There are two ways to establish the first and second claims. One is by using the interpretation of R_0 in terms of the lifespan and productivity of each stage. The other is by computing the eigenvalues the Jacobian. We briefly sketch the first approach. In the absence of immune response, stage 0 has an expected lifespan of $\frac{1}{a_0+f_0}$. During that time, it produces $\frac{r_0 f_0}{a_0+f_0}$ copies of stage 1. These, in turn, produce $\frac{r_0 f_0}{a_0+f_0} \frac{r_1 f_1}{a_1+f_1}$ copies of stage 2. Continuing in this way produces R_0 copies of stage 0. If this is greater than 1, the pathogen can establish infection, if less than 1, not.

To see these two claims using the eigenvalues of the Jacobian, notice that since $\varphi_j(0) = 0$, $j = 0, ..., n-1$, the Jacobian matrix evaluated at $(S^*, T^*) = (\vec{0}, \vec{0})$ is identical to the one obtained in [5, Proposition 1]. Thus the claim follows from Propositions 1 and 2 of [5].

The third claim comes from showing that the reproductive number in the presence of immune response is no more than the reproductive number in the naive host as in [5, Proposition 1]. □ □

The following correspond to the numbered observations in Section 3 of [5] and follow from the fixed point equations

$$\dot{S}_j = \widehat{F}_j(S^*, T^*) = r_{j-1} f_{j-1} S^*_{j-1} - S^*_j(a_j + f_j + T^*_j) = 0$$
$$\dot{T}_j = \widehat{G}_j(S^*, T^*) = (\varphi_j(S^*_j) - b)T^*_j = 0$$

1) Given (S^*, T^*), if there is j such that $S^*_j = 0$ then $(S^*, T^*) = 0$.
2) If $j \in \mathrm{Reg}(S^*, T^*)$, then $S^*_j = b_j$.
3) If $j \in \mathrm{Unreg}(S^*, T^*)$, then $T^*_j = 0$.
4) If $j+1 \in \mathrm{Unreg}(S^*, T^*)$, then $S^*_{j+1} = S^*_j M_j$.
5) If $[j+1, k] \subset \mathrm{Unreg}(S^*, T^*)$ then $S^*_k = S^*_j M_{jk}$. This follows by induction on the previous observation.
6) Assume $\mathrm{Reg}(S^*, T^*) \neq \emptyset$. If $k \in \mathrm{Unreg}(S^*, T^*)$, then $S^*_k = b_{h_k} M_{h_k k}$. This follows from 2) and 5).
7) If θ is generic and $(S^*, T^*) \neq 0$ then $\mathrm{Reg}(S^*, T^*) \neq \emptyset$. Were $\mathrm{Reg}(S^*, T^*) = \emptyset$, then by 5) $S^*_0 = S^*_0 R_0$. Consequently $R_0 = 1$, contradicting our first genericity requirement.
8) If $j \in \mathrm{Reg}(S^*, T^*)$ then $T^*_j = \frac{r_{j-1} f_{j-1}}{b_j} S^*_{j-1} - (a_j + f_j)$.
9) If $j \in \mathrm{Reg}(S^*, T^*)$ then $T^*_j = r_{j-1} f_{j-1} \frac{b_{h_j}}{b_j} M_{h_j j-1} - (a_j + f_j)$. This follows from the fact that $S^*_{j-1} = S^*_{h_j} M_{h_j j-1}$ (which follows from 6) if $j-1 \in \mathrm{Unreg}(S^*, T^*)$, and holds trivially, if $j-1 \in \mathrm{Reg}(S^*, T^*)$) and $S^*_{h_j} = b_{h_j}$.
10) If $j \in \mathrm{Reg}(S^*, T^*)$, then $T^*_j > 0$ if and only if $b_{h_j} M_{h_j j} > b_j$. This follows from the previous observation; (recall that we have assumed $\mathrm{SE}(\theta) = \emptyset$).

Proposition 14. *Suppose θ is generic and (S^*, T^*) is a biologically meaningful fixed point. Suppose further that $j \succ k$. If $j \in$ Reg(S^*, T^*), then $k \in$ Unreg(S^*, T^*).*

Proof. Suppose $j \succ k$ and $j \in \mathrm{Reg}(S^*, T^*)$. Let $\{j = j_0, j_1, \ldots, j_m\} = [j, k) \cap \mathrm{Reg}(S^*, T^*)$ (cyclically ordered as listed) and let $j_{m+1} = k$. If $m = 0$, then, $h_k = j$ and, due to $j \succ k$, it holds $b_{h_k} M_{h_k k} < b_k$. Thus, the claim follows by observation 10), above. Otherwise we have $j \neq j_m = h_k$ and it suffices to show that $S^*_{j_m} M_{j_m k} < b_k$. For $\ell = 0, \ldots, m$, we have $j_\ell \in \mathrm{Reg}(S^*, T^*)$ so we must have $S^*_{j_\ell} = b_{j_\ell}$. For $\ell = 0, \ldots, m-1$ we must also have $S^*_{j_{\ell+1}} < S^*_{j_\ell} M_{j_\ell j_{\ell+1}}$, because $h_{j_{\ell+1}} = j_\ell$. We then have

$$\begin{aligned} b_{j_1} &= S^*_{j_1} < S^*_{j_0} M_{j_0 j_1} \\ b_{j_2} &= S^*_{j_2} < S^*_{j_1} M_{j_1 j_2} < S^*_{j_0} M_{j_0 j_2} \\ &\vdots \\ b_{j_m} &= S^*_{j_m} < S^*_{j_0} M_{j_0 j_m} = b_{j_0} M_{j_0 j_m} \end{aligned}$$

so that

$$S^*_{h_k} M_{h_k k} = S^*_{j_m} M_{j_m k} < b_{j_0} M_{j_0 k} < b_k.$$

Thus $k \in \mathrm{Unreg}(S^*, T^*)$ as required. □ □

Proposition 15. *Let θ be a generic parameter set such that $R_0 > 1$. Then $\succ$ is a strict partial order.*

Proof. We must show that $\succ$ is anti-reflexive, asymmetric and transitive. The first follows immediately from the fact that $M_{jj} = 1$.

To see that $\succ$ is asymmetric, suppose we have $j \succ k$ and $k \succ j$. We then have $b_j M_{jk} < b_k$ and $b_k M_{kj} < b_j$. This gives $b_j > b_j M_{jk} M_{kj}$. But $M_{jk} M_{kj} = R_0$, contradicting $R_0 > 1$.

To see the third we suppose that $j \succ k$ and $k \succ \ell$. We consider two cases, $k \in [j, \ell]$ and $\ell \in [j, k]$. In the first case, we have $M_{jk} M_{k\ell} = M_{j\ell}$. We then have $b_j M_{jk} < b_k$, $b_k M_{k\ell} < b_\ell$ giving $b_j M_{j\ell} = b_j M_{jk} M_{k\ell} < b_k M_{k\ell} < b_\ell$ as required. In the second case, we have $M_{jk} M_{k\ell} = R_0 M_{j\ell}$, so that $b_j R_0 M_{j\ell} = b_j M_{jk} M_{k\ell} < b_k M_{k\ell} < b_\ell$. Since $R_0 > 1$, this implies $j \succ \ell$ as required. □ □

Remark 16. Since $\succ$ is a partial order, it is cycle-free, that is there is no sequence of stages $j_0 \succ j_j \succ \ldots \succ j_0$. Consequently, we can define the *depth* of a stage k, $d(k)$ to be the length of the longest chain $j_0 \succ \ldots \succ j_{d(k)} = k$. It follows that $\mathrm{Unstr}(\theta)$ consists of the stages of depth 0. In particular, $\mathrm{Unstr}(\theta) \neq \emptyset$. Note that if θ is such that no two stages are comparable, then $\succ$ is empty and every stage is $\succ$-maximal, so $\mathrm{Unstr}(\theta) = [0, n)$. $\mathrm{Str}(\theta)$ consists of the stages of positive depth. If $\mathrm{Incomp}(\theta) \neq \emptyset$, $\mathrm{Incomp}(\theta)$ consists of the stages of maximal depth.

Proposition 17. *Suppose that θ is generic. Furthermore, let (S^*, T^*) be a biologically meaningful infected fixed point. Then the pathogen populations are moderated at (S^*, T^*) if and only if the immune response is saturated at (S^*, T^*).*

Proof. We first show that if (S^*, T^*) is moderated, then (S^*, T^*) is saturated.

We claim $\mathrm{Unstr}(\theta) \subseteq \mathrm{Reg}(S^*, T^*)$. Suppose to the contrary $j \in \mathrm{Unstr}(\theta) \cap \mathrm{Unreg}(S^*, T^*)$. By assumption (S^*, T^*) is moderated, so $S_j^* < b_j$. Since $j \in \mathrm{Unreg}(S^*, T^*)$, by 7), 6) and 2) above, $S_j^* = S_{h_j}^* M_{h_j j} = b_{h_j} M_{h_j j}$. This gives $b_{h_j} M_{h_j j} < b_j$, i.e., $h_j \succ j$, contradicting the assumption that $j \in \mathrm{Unstr}(\theta)$. This proves the claim.

We claim that $\mathrm{Str}(\theta) \subseteq \mathrm{Unreg}(S^*, T^*)$. If $\mathrm{Str}(\theta) = \emptyset$, this holds trivially. Suppose $k \in \mathrm{Str}(\theta)$. Then there is a maximal j so that $j \succ k$. Being maximal $j \in \mathrm{Unstr}(\theta)$ and thus $j \in \mathrm{Reg}(S^*, T^*)$. It follows by Proposition 14 that $k \in \mathrm{Unreg}(S^*, T^*)$ as required.

We now show that if (S^*, T^*) is saturated, then (S^*, T^*) is moderated.

If $\mathrm{Unreg}(S^*, T^*) = \emptyset$, the claim holds vacuously. Suppose that $k \in \mathrm{Unreg}(S^*, T^*)$. We must show that $S_k^* < b_k$. Again, we choose j to be maximal so that $j \succ k$. Since (S^*, T^*) is saturated, $j \in \mathrm{Reg}(S^*, T^*)$, thus, by 2) $S_j^* = b_j$. If $[j + 1, k) \subseteq \mathrm{Unreg}(S^*, T^*)$, we are done, for then $S_k^* = S_j^* M_{jk} = b_j M_{jk} < b_k$. On the other hand if $[j + 1, k) \cap \mathrm{Reg}(S^*, T^*) \neq \emptyset$, choose $m \in [j + 1, k) \cap \mathrm{Reg}(S^*, T^*)$ so that $m = h_k$. Since $m \in \mathrm{Reg}(S^*, T^*)$, by the assumed saturation $m \in \mathrm{Unstr}(\theta)$. Therefore $j \not\succ m$, in other words, $b_j M_{jm} \geq b_m$. If $b_m M_{mk} \geq b_k$, these two inequalities would yield $b_j M_{jk} = b_j M_{jm} M_{mk} \geq b_k$ contradicting $j \succ k$. Consequently $b_m M_{mk} < b_k$ must hold. Now we have $S_k^* = S_m^* M_{mk} = b_m M_{mk} < b_k$ as required. □ □

Theorem 18. *Suppose θ is generic and (S^*, T^*) is a biologically meaningful infected fixed point which is not saturated. Then there is $j \in Unreg(S^*, T^*)$ so that for any open neighborhood U of (S^*, T^*) there is a biologically meaningful point $x \in U$ so that $\frac{dT_j}{dt}\big|_x > 0$. In particular (S^*, T^*) is unstable.*

Proof. Since (S^*, T^*) is not saturated, it is not moderated. Thus, there is $j \in \mathrm{Unreg}(S^*, T^*)$ with $S_j^* \geq b_j$. Since θ is generic, $S_j^* > b_j$, for otherwise we would have $b_{h_j} M_{h_j j} = b_j$. In particular, $b_j < \infty$. It follows that $j \notin \mathrm{Incomp}(\theta)$. Since $S_j^* > b_j$, $\varphi_j(S_j^*) > b$, so $\frac{\partial \widehat{G}_j}{\partial T_j}|_{(S^*, T^*)} = \varphi_j(S_j) - b > 0$.

Let e_{T_j} be the unit vector in the T_j direction. Then, for any $\delta > 0$, $\dot{T}_j|_{(S^*,T^*)+\delta e_{T_j}} > 0$. Thus, in any open neighborhood U of (S^*, T^*), there are biologically meaningful points whose orbits move away from (S^*, T^*). In particular, (S^*, T^*) is unstable as required. □ □

Theorem 19. *Suppose that θ is generic and that (S^*, T^*) is a biologically meaningful infected fixed point. In particular, not all T_j^* are equal. If (S^*, T^*) is moderated then (S^*, T^*) is a local asymptotically stable equilibrium. In particular, the eigenvalues of the Jacobian matrix $J(S^*, T^*)$ have strictly negative real part.*

Corollary 20. *For a generic parameter set, the system (3) (and hence (2)) has a unique biologically meaningful stable fixed point.*

Proof. Since the sets of starvable and unstarvable stages depend only on θ, there is exactly one saturated fixed point, hence exactly one moderated fixed point. The Corollary now follows from the Theorem. □ □

Theorem 19. The proof of the corresponding Theorem in [5] proceeds by showing that the Jacobian matrix of the system (4) has eigenvalues all of whose real parts are negative. It will therefore suffice to show that we can carry out the same computation on the Jacobian matrix of (3) evaluated at a moderated fixed point (S^*, T^*). Since H and $\widehat{H}$ are identical, we need only consider the partials of G and $\widehat{G}$. We have

$$\frac{\partial G_k}{\partial S_j} = \begin{cases} T_k & \text{if } j = k \\ 0 & \text{otherwise} \end{cases}$$

$$\frac{\partial \widehat{G}_k}{\partial S_j} = \begin{cases} \varphi_k'(S_k)T_k & \text{if } j = k \\ 0 & \text{otherwise} \end{cases}$$

Now for $k \in \text{Unreg}(S^*, T^*)$, both of these partial derivatives vanish, while if $k \in \text{Reg}(S^*, T^*)$, We then have $S_k^* = b_k$ so that $\varphi_k'(S_k^*) = 1$, and once again, the two are identical.

Moreover, we have

$$\frac{\partial G_k}{\partial T_j} = \begin{cases} S_k - b & \text{if } j = k \\ 0 & \text{otherwise} \end{cases}$$

$$\frac{\partial \widehat{G}_k}{\partial T_j} = \begin{cases} \varphi_k(S_k) - b & \text{if } j = k \\ 0 & \text{otherwise} \end{cases}$$

Now if $k \in \text{Reg}(S^*, T^*)$, we have $S_k^* = b$ so that $S_k - b = 0$ in the former case, while in the latter case we have $S_k^* = b_k$ so that $\varphi_k(S_k^*) - b = 0$. Finally, in the case where $k \in \text{Unreg}(S^*, T^*)$, the proof of [5, Theorem 2] appeals to the fact that (S^*, T^*) is moderated, thus ensuring that $S_k^* - b < 0$. Here, the fact that (S^*, T^*) is moderated implies that $S_k^* < b_k$ so that $\varphi_k(S_k^*) - b < 0$ and we can proceed as before. □ □

3.1. **Self-establishing stages.** We now turn to the case where $\text{SE}(\theta) \neq \emptyset$. In this case we need the assumption that θ is not fatal, that is, $\text{SE}(\theta) \cap \text{Incomp}(\theta) = \emptyset$ and $\text{Incomp}(\theta) \neq [0, n)$.

We start by observing that if $\text{SE}(\theta) \neq \emptyset$, then the pathogen is viable. Accordingly, in place of Proposition 13, we have the following.

Proposition 21. *If $SE(\theta) \neq \emptyset$, then $(S^*, T^*) = (0, 0)$ is an unstable equilibrium. In particular, the pathogen is able to infect the host.*

Proof. Suppose that $j \in \mathrm{SE}(\theta)$. Then $\frac{\partial \widehat{F}_j}{\partial S_j}|_{(0,0)} = -a_j - f_j > 0$. This gives orbits with positive and increasing S_j inside any open set around $(0,0)$. □ □

The numbered observations 1) through 9) listed above hold without change. Observation 10) now requires the additional hypothesis that $j \notin \mathrm{SE}(\theta)$, giving

10′) If $j \in \mathrm{Reg}(S^*, T^*)$ and $j \notin \mathrm{SE}(\theta)$, then $T_j^* > 0$ if and only if $b_{h_j} M_{h_j j} > b_j$.

As before, this follows from observation 9).

Proposition 22. *Suppose that SE(θ) $\neq \emptyset$ and (S^*, T^*) is a biologically meaningful infected fixed point. Then SE(θ) $\subseteq$ Reg(S^*, T^*).*

Proof. This follows from noting that $j \in \mathrm{SE}(\theta)$, $S_j^* > 0$ and $T_j^* = 0$ implies $\dot{S}_j > 0$. □ □

Proposition 23. [2] *Suppose SE(θ) $\neq \emptyset$. Then $\succ$ is a strict partial order.*

Proof. We must show that $\succ$ is anti-reflexive, asymmetric and transitive. The first follows immediately from the fact that $M_{jj} = 1$.

To see that $\succ$ is asymmetric, suppose we have $j \succ k$ and $k \succ j$. This implies $(j,k] \cap \mathrm{SE}(\theta) = \emptyset$ and $(k,j] \cap \mathrm{SE}(\theta) = \emptyset$, contradicting $\mathrm{SE}(\theta) \neq \emptyset$.

To see the third we suppose that $j \succ k$ and $k \succ \ell$. We consider two cases, $k \in [j, \ell]$ and $\ell \in [j,k]$. In the first case, we have $M_{jk} M_{k\ell} = M_{j\ell}$. We then have $b_j M_{jk} < b_k$, $b_k M_{k\ell} < b_\ell$ giving $b_j M_{j\ell} = b_j M_{jk} M_{k\ell} < b_k M_{k\ell} < b_\ell$ as required. The second case would imply $(j,k] \cup (k,\ell] = [0,n)$ as well as $(j,k] \cap \mathrm{SE}(\theta) = \emptyset$ and $(k,\ell] \cap \mathrm{SE}(\theta) = \emptyset$, contradicting $\mathrm{SE}(\theta) \neq \emptyset$. □ □

We define Str(θ), Unstr(θ), saturated and moderated as before. Proposition 14 holds in the case $\mathrm{SE}(\theta) \neq \emptyset$. However, there is a small change in the proof. In the case where $\mathrm{SE}(\theta) = \emptyset$, we appeal to observation 10). In the case where $\mathrm{SE}(\theta) \neq \emptyset$, we need to note that $j \succ k$ implies that $k \notin \mathrm{SE}(\theta)$ and we are thus able to appeal to observation 10′. The proof then proceeds as before.

The equivalence of moderation and saturation (Proposition 17) and their necessity for stability (Theorem 18) can be proved as before, the result of Proposition 22 playing an important role.

In order to prove sufficiency in the presence of self-establishing stages (Theorem 19 and its consequences), we rely on Lemma 1 of Section 8 in [5] and the argument provided there after the Proof of the Lemma.

4. Discussion

In this paper, we have generalized the T-cell activation and proliferation model of [5] in order to make that model applicable to more realistic antigen dose - T-cell proliferation response curves. While in most regimes, we would expect T-cell proliferation to rise in response to increased antigen, this rate is not driven by the encounter of T-cells with infected target cells, but rather by the presentation of antigen to T-cells by dendritic cells ([12]). Thus, a model of the mechanisms underlying T-cell proliferation must include additional cell populations and quite complicated cellular processes carried out by those cells ([18]).

Further, there is a widespread phenomenon that cannot be explained as the fixed point of a system like (3), namely the existence of long-lived T-cell responses to multiple epitopes, either of a single pathogen or in our case to a single pathogen stage. Multiple T-cell responses are often

[2] We take the opportunity to amend Proposition 7 of Section 8 in [5]. The condition $R_0 > 1$ in the statement of that proposition is not required, given that we take $\mathrm{SE}(\theta) \neq \emptyset$ as a standing assumption for the entire Section 8.

modeled as competing for antigen in a predator-prey dynamic. The antigenicity of the T-cell's epitope functions as the T-cell's fitness and this leads to a winner-take-all dynamic where the response to the most antigenic epitope survives and the others become extinct ([13], [17]). It seems likely that memory T-cells play an important role in the survival of multiple responses. However, the interactions between effector and memory populations are still not well understood ([4], [1]). These populations exhibit differing longevity. Stated in terms of our model, they do not share a common value for b. In addition, high levels of antigen can lead to CTL exhaustion ([11]), a phenomenon that argues against a monotone increasing φ.

The upshot of this is that if we wish to refine the cyclic pathogen model to present an increasingly detailed picture of the cell populations and their mechanisms, we will need to include multiple immune cell populations at each stage. The dynamics of such a system could be quite complicated. However, there is a variable that summarizes the collective immune pressure against a given stage, namely their net kill rate of the effector populations. Thus, if $T_{j1}, \ldots, T_{jk}$ are the effector populations against stage S_j, we can write $\tau_j = \tau_j(T_{j1}, \ldots, T_{jk})$ so that we now have

$$\frac{dS_j}{dt} = r_{j-1} f_{j-1} S_{j-1} - (a_j + f_j + \tau_j) S_j.$$

We cannot expect that the dynamics of such an expanded system can be mapped to the dynamics of (3) because we cannot necessarily expect $T_{j1}, \ldots, T_{jk}$ (and any non-effector populations) to vary in a way which makes $\frac{d\tau_j}{dt}$ a function of S_j and τ_j. However, once the dynamics of these populations are understood, in the neighborhood of a fixed point, understanding the marginal response of τ_j to S_j may allow us to use (3) to summarize these dynamics in a way which will allow us to establish the existence of a stable fixed point.

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Pathology Department, Tufts University, Boston, MA USA
E-mail address: michael.shapiro@tufts.edu

Children's Hospital (UKBB), University of Basel, Spitalstr. 33, Postfach, 4031 Basel, Switzerland
E-mail address: edgar.delgado-eckert@bsse.ethz.ch